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Since writing to you on 28 January 1955 we have completed experiments on the blocking of LSD-reaction with Reserpine, a combination of LSD with C-9, and tolerance to LSD by prior administration of LAE. Some further information is available on C-9, and studies designed to shed light on the characteristics of the mental effects induced by C-9 are underway. Trials for the blockade of LSD-reaction with "Frenquel" (4-piperdyl-diphenyl-carbinol) are in progress and will soon be complete. Experiments are being carried on with cohoba snuff, but to date no reaction has been observed in the doses used. More details of the descriptions of the experiments together with tables are given below.

Reserpine as LSD Blocking Agent.

In this experiment 12 negro subjects received the following combinations of drugs: (1) Reserpine placebo-LSD placebo; (2) Reserpine placebo-LSD; (3) LSD placebo-Reserpine; (4) LSD-Reserpine. Reserpine was given orally in a dose of 1 mg. ten hours, and 1 mg. two hours prior to administration of the LSD placebo, or 60 mcgm. of LSD. Placebos used for Reserpine were identical in appearance with tablets of the active drug. Experiment was conducted in double-blind fashion. Measurements were those previously described from this laboratory (estimation of knee jerk, measurement of pupillary size, measurement of systolic blood pressure, administration of questionnaire, hourly assessment of clinical grade of reaction). Data were analyzed by same methods explained in previous reports.

It can be seen from the table that Reserpine caused no significant change in any of these measures. We therefore concluded that, in this dose, Reserpine does not block the LSD-reaction. It might be desirable to repeat this work using a larger dose of Reserpine and a longer period of administration prior to testing with LSD. Of interest, however, is the fact that definite side effects were observed even with the small doses of Reserpine used.

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LAE-32 as Blocker of LSD-25 Effect.

Since LAE-32 is a relatively impotent drug which structurally is closely related to LSD-25 it was felt that prior administration of a dose of LAE might block the receptor sites and thereby prevent or modify the LSD-reaction. Twelve negro patients were, therefore, given in randomized order under double-blind technique: (1) LAE placebo followed by LSD placebo; (2) LAE placebo followed by 60 mcgm. LSD; (3) LAE, 500 mcgm. followed by LSD placebo; (4) LAE, 500 mcgm., followed in one hour by LSD, 60 mcgm. The LAE-32 used in these experiments was in the form of enteric-coated pills rather than in the form of solution in ampules. Suggestive evidence of very mild LSD-like effects was observed in these subjects with this dosage of LAE. The effects, however, were not significantly different statistically from those obtained with placebo (see table) Also, there was no significant difference between placebo-LSD and LAE-LSD, although a mild trend toward reduction of the LSD reaction was observed which was not sufficiently great to warrant further exploration.

Cross Tolerance Between LAE-32 and LSD-25.

This experiment was carried out at the suggestion of Dr. Harold Abramson in the hope that one might develop tolerance to LSD without incurring the unpleasant side effects associated with development of tolerance with administration of LSD. Twelve negro patients, therefore, received in randomized order by the double-blind technique: (1) LAE placebo for one week; (2) LAE, 500 mcgm., for three days, followed by 1000 mcgm. LAE for four days. Patients were then tested with the standard dose (60 mcgm.) LSD-25. It was not felt that it was necessary to do the placebo-placebo and placebo-LAE controls at this time, since they were fairly well covered by the first experiment. Methods of measurement of the LSD-reaction and analyzing the data were the same as previously reported.

During the week of administration of LAE-32 definite but mild LSD-like effects were reported by the patients. We have the impression that these were as unpleasant as the effects of LSD-25, given by one of the schedules we have used to develop tolerance in the past. As can be seen by the table, there was a definite tendency for the intensity of the LSD-reaction to be reduced following a weeks administration of LAE. Significant reduction in knee jerks, pupillary size and systolic blood pressure were observed and there were nearly significant reductions in the number of answers to questionnaire and in the clinical grade of effect. It would appear that some degree of tolerance did develop. Tolerance, however, was far less than that induced by repeated administration of LSD. This method, therefore, does not seem to be a very practical way of inducing tolerance to LSD.

Reproducibility of the LSD-25 Response.

In the course of the experiments described above three trials of the effect of 60 mcgm. of LSD were carried out on the same 12 patients under nearly identical conditions. As can be seen from the table on reproducibility of the LSD-response, the LSD-reaction is an extremely consistent biological phenomenon. Reproducibility is, of course, very important in testing the effects of various antidotal drugs.

Combination of LSD-25 with C-9.

The purpose of this experiment was to study possible enhancement of blocking of the LSD-response by combining the drug with C-9. The same 12 patients who were used in the LAE and Reserpine experiments received in randomized order according to the double-blind technique: (1) C-9 placebo-LSD placebo; (2) C-9 placebo-LSD-25; (3) LSD placebo-0.5 mg. C-9; (4) LSD, 60 mcgm., -0.5 mg. C-9; (5) LSD, 60 mcgm., -1 mg. C-9.

In addition to the usual LSD measurements (pupillary size, estimation of knee jerks, measurement of resting blood pressure, LSD questionnaire, and assessment of clinical grade), the pulse rate and systolic blood pressure of these patients were measured at one-minute intervals for five minutes after assuming the standing position. All measurements were made prior to administration of the drugs and once per hour for eight hours after administration of the drugs. It was realized that the observation period was not sufficiently long, but circumstances prevented extension of the observation period for more than eight hours after administration of the drug.

Results are shown in the table. It should be noted that a significant number of answers on the questionnaire occurred with administration of C-9. Analysis of the answers showed, however, a very different pattern from that seen after LSD dose. High scores were obtained on a group of symptoms resembling those seen after administration of Atropine (decreased salivation, dryness of mouth, dry taste in mouth), and on such questions as increase in auditory acuity, drowsiness, and hunger. The familiar LSD-pattern of anorexia, nervousness, insomnia, plus visual perceptual distortion was not observed.

The cardiovascular effects of C-9 were apparent even with the 0.5-mg. dose (see table). Insofar as the data permit analysis, C-9 did not block or accentuate the effects of LSD on the pupils, knee jerks or resting blood pressure. C-9 did block in part the rise in blood pressure on standing after LSD alone. LSD, on the other hand, partially blocked the drop in blood pressure on standing seen after 0.5 mg. C-9 alone.

It may be desirable when conditions permit to study the combination of LSD and C-9 more intensively, using larger doses of LSD and prolonging the period of observation to at least 16 hours. Before this can be done, it will be necessary to develop a method of differentiating between mental effects caused by C-9 and mental effects caused by LSD as well as a method of grading the effects of both.

"Frenquel" as Intravenously as a Reverser of the LSD-Reaction.

A few preliminary experiments of this kind have been carried out. Four patients received in randomized order: (1) 60-75 mgm. followed in two hours by 15-25 mg. Frenquel iv; (2) 60-75 mcg. LSD followed in two hours by a Frenquel placebo intravenously; (3) LSD placebo followed in two hours by 25 mg. of Frenquel intravenously. Frenquel alone induced no measureable drug effects. There were no obvious differences in the intensity and course of the LSD-reaction in these patients on the Frenquel trial as compared with the placebo trial. While the number of patients is small, results do not justify extensive exploration of the antidotal effect of "Frenquel."

Administration of Frenquel Orally for One Week as a Blocker of LSD-Reaction.

Twelve negro subjects received the following combinations of drugs: (1) Frenquel placebo-LSD placebo; (2) Frenquel placebo-60 mcgm. LSD; (3) Frenquel-LSD placebo; (4) Frenquel-LSD. Frenquel (and Frenquel placebo) was administered orally in doses of 20 mg. three times daily for six days prior to administration of LSD or LSD placebo. Procedure was carried out in double-blind fashion. The purpose of the experiment was not explained to the patients. One weeks time was allowed to elapse between administration of Frenquel and Frenquel placebo to permit "washout" of any Frenquel that might have been given previously. Methods of assessing the LSD-reaction were the same as those reported above.

Although the experiment is not yet complete and the code has not been broken, results so far strongly suggest that we will be unable to distinguish between Frenquel and placebo. Another report will be submitted as soon as possible when the work is complete.

Miscellaneous Information on C-9.

(1) Stability. The alcoholic solution of the original lot of C-9 has been kept for almost a year. This material is apparently as effective as when first received.

(2) Method of Administration. C-9 appears to be equally effective when given on food, in coffee, in soft drinks, or in alcoholic drinks. It is also effective when smoked (see letter of 28 January 1955), although larger amounts of the drug are required and the results are more erratic.

(3) Comparison of Cardiovascular Effects of C-9 with those of Marihuana and Parahexyl. The same kind of cardiovascular effects (tachycardia at rest, tachycardia and postural hypotension on standing) occur after administration of an alcoholic extract of marihuana orally, after smoking of marihuana cigarettes, and after 45 mg. of parahexyl orally, as after the administration of C-9. The cardiovascular effects of C-9 are probably common to all active members of the cannabinol group.

(4) Mental Effects of C-9. Effort is now underway to obtain a better delineation of the effects induced by C-9. The subjective sensations induced by the marihuana group have long been obscure. The descriptions in most of the writings on marihuana with respect to the occurrance of vivid, depersonalized, hallucinatory or cataleptic states have seldom been observed when these drugs have been studied under controlled institutional conditions. Ordinarily the subjective effects induced by marihuana in such circumstances appear to be rather mild, and so far descriptions given by institutionalized patients have not shed a great deal of light on the exact nature of the sensations experienced. For this reason, 12 patients were given a sentence-completion test, consisting of incomplete sentences chosen to yield information with respect to mental status (affect, mood, bizarre thinking, etc), and somatic symptoms (dryness of the mouth, blurring of vision, changes in auditory acuity, etc). Validating questions and general drug questions are also included. Incomplete sentences which elicited consistently positive responses were selected from this original test and a new true-false test consisting of over 300 items constructed. This true-false test is now being administered to 30 men. When the results are in, item analysis will be carried out and further work conducted based on leads obtained from the high scoring items.

(5) Preliminary Clinical Description of the C-9 Reaction. A description of the C-9 reaction based on observations made in 33 trials of 1 to 2.5 mg. of C-9 orally in 17 subjects has been prepared and is appended. It should be borne in mind that this description is preliminary in nature and may have to be modified greatly as further information is accumulated.

Future Plans.

In addition to studies on the C-9 reaction, future plans include studies of the effect of combinations of Scopolamine and LSD-25, the use of Reserpine as a quieting drug, and the testing of new substances from the University of Illinois as they become available.

Very sincerely yours,

Harris Isbell

Harris Isbell, M.D.
Director of Research

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Enclosures

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EFFECTS OF 1 MGM. RESERPINE 10 HOURS AND 2 HOURS PRIOR TO 60 MCGM. LSD-25

E[illegible]RE	DRUG			
	PLACEBO-PLACEBO	PLACEBO-LSD	PLACEBO-RESERPINE	RESERPINE-LSD
nee Jerk	↓ 0.62	↓ 3.31 P	↓ 1.02	3.10 P
upillary Size	↓ 0.35	↓ 3.02 P	↓ 0.31	3.35 P
lood Pressure	↓ 0.75	↓ 2.39 P	↓ 0.60	1.99 P
uestions	12	93 P	14	101 P
linical Grade	0	1.5 P	0	1.5 P

ethod of analyzing data same as in prior reports.

Indicates significant difference statistically from placebo.

p[illegible] of differences between Placebo-LSD and Reserpine-LSD are significant.

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EFFECTS OF LAE-32 (500 MCGM.) GIVEN ONE HOUR BEFORE 60 MCGM. OF LSD-25

MEASURE	DRUG			
	PLACEBO-PLACEBO	PLACEBO-LSD	PLACEBO-LAE	LAE-LSD
Knee Jerk	± 0.62	± 3.32 P	± 1.26	± 2.46P
Pupillary Size	± 0.35	± 3.02 P	± 0.67	± 2.91P
Blood Pressure	± 0.75	± 2.40 P	± 0.56	± 1.96P
Number of Questions	12	101 P	32	78P
Clinical Grade	0	1.5 P	0.3	1.2 P

LAE or Placebo given at 0700 a.m.; LSD given at 0800 a.m. Figures are averages on 12 subjects.

P indicates difference significant statistically from placebo-placebo.

Differences between placebo-placebo and placebo-LAE not significant.

Differences between placebo-LSD and LAE-LSD not significant.

COMPARISON OF LSD-25 EFFECTS AFTER A WEEK OF PLACEBO AND AFTER A WEEK OF LAE-32

MEASURE	DRUG		DIFFERENCE	[illegible] OF DIFFERENCE
	PLACEBO-LSD	LAE-LSD		
Knee Jerk	↓ 3.01	↓ 2.18	- 0.83	>0.05
Pupillary Size	↓ 3.73	↓ 2.46	- 1.27	<0.01
Systolic Blood Pressure	↓ 2.30	↓ 1.03	- 1.27	<0.01
Questions	97	75	- 22	>0.1
Clinical Grade	1.1	0.8	- 0.3	>0.1

Figures are averages on 12 subjects. Method of analyzing data same as in previous reports.

STATISTICAL REPRODUCIBILITY OF LSD-25 RESPONSE

MEASURE	TRIAL 1	TRIAL 2	TRIAL 3
Knee Jerk	3.32 ± 0.47	3.01 ± 0.38	3.31 ± 0.52
Pupillary Size	3.02 ± 0.20	3.73 ± 0.27	3.02 ± 0.18
Blood Pressure	2.40 ± 0.36	2.30 ± 0.18	2.39 ± 0.38
Questions	101 ± 24	97 ± 29	93 ± 19
Clinical Grade	1.5 ± 0.32	1.1 ± 0.3	1.5 ± 0.11

Figures are means of values on 12 subjects ± standard errors.

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EFFECTS OF COMBINING 60 MCGM. LSD-25 WITH 0.5 MGM. AND 1.0 MGM. C9

MEASURE	DRUG				
	PLACEBO-PLACEBO	PLACEBO-LSD	PLACEBO-0.5 C9	LSD-+0.5 C9	LSD-1.0 C
Knee Jerk	+ 0.62	+ 3.32 P	+ 1.41	+ 2.88 P C	+ 2.96 P
Pupillary Size	+ 0.35	+ 3.02 P	- 0.08	+ 2.70 P C	+ 3. P
Resting Blood Pressure	+ 0.75	+ 2.40 P	+ 0.49	+ 2.19 P C	+ 2.10
Questions	12	101 P	56 P	94 P	87 P
Clinical Grade	0	1.5	0.3	1.2 P	1.2
Standing Pulse Rate	90	99	112 P	105 P	116 P
Standing Blood Pressure	109	119	97 P	107 L C	102 L

P - Figure significantly different from Placebo-Placebo.

C - Figure significantly different from Placebo-C9.

L - Figure significantly different from Placebo-LSD.

Figures are means of results on 12 patients. Placebo-Placebo and Placebo-LSD figures also used in LAE experiment.

Data in top 5 measures analyzed as in previous reports.

Data on "standing" pulse rates and "standing" blood pressures obtained once per minute for 5 minutes after standing. Values totalled for 5-minute period and then totalled for each observation. Final figure divided by number of minutes (5)x number of observations (8) to attain average for day. Means of daily averages then calculated as usual.

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